HIGH PREVALENCE OF LOW BONE MASS IN ADOLESCENTS WITH NON-TRANSFUSION DEPENDENT HEMOGLOBIN E/β THALASSEMIA

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The authors declare no conflict of interest.

Background

- Hb E/β thalassemia is the most common β thalassemia syndrome in Asia-Pacific region due to a high prevalence of Hb E and β thal genes.
- Management of this condition can be cumbersome due to its clinical heterogeneity and various disease severity ranging from severe end in which patients are transfusion dependent (TD) thalassemia similar to that of β thal major (TM) to moderate and mild severity which are non-transfusion dependent (NTD) thalassemia akin to β thal intermedia.
- The natural history and disease related complications among patients with Hb E/β thalassemia can vary greatly due to different baseline severity and management received. In 2013, the Thalassaemia International Federation (TIF) has developed a clinical practice guideline for NTD patients, however, most recommendations used were based on studies in β-thal intermedia but only few were derived from Hb E/β thalassemia.
- For example, endocrinopathies associated with iron overload such as adrenal insufficiency, vitamin D deficiency and low bone mass are highly prevalent among TD patients but little is known about NTD patients.
- While NTD patients were previously considered to have low risks of endocrinopathies. Our group has recently shown the high prevalence of adrenal and vitamin D insufficiency in NTD patients[1,2]. This suggests that these NTD patients are highly susceptible to endocrinopathies like TD patients or even greater.
- Since there are limited data on bone mineral density (BMD) among NTD thalassemic population and non for NTD Hb E/β thalassemia. Therefore it is of important to evaluate bone health using BMD measurement by Dual Energy X-ray Absorptiometry (DXA) among NTD patients

Objective

- To determine the prevalence of low bone mass in NTD Hb E/β thalassemic adolescents and factors relating with low bone mass among these patients

Subjects and Methods

- 22 adolescents (13 boys and 9 girls) aged 13.2 to 20 years with NTD Hb E/β-thalassemia were studied. They had received either no or occasional transfusion.
- Blood samples were collected to determine hemoglobin, serum ferritin, serum 25-hydroxyvitamin D (25-OHD), labile plasma iron (LPI), and non-transferrin bound iron (NTBI).
- Bone age X-ray of the left hand was performed and the readings were compared with X-ray photographs from the Atlas of Greulich and Pyle.
- BMD of the lumbar spines (L2-L4; BMDLS) and total body (BMDTB) were measured by DXA (Lunar Prodigy, Lunar Corp., USA). BMD values were compared with normal BMD reference for Thai children (age and gender-matched) and expressed as Z-score[3].
- Since delayed bone age, commonly found in thalassemic children, results in smaller bone size and decreases apparent areal BMD, the BMD Z-score for chronological age would be underestimated. Therefore the BMD Z-score adjusted for bone age was calculated.

Interpretation of BMD values (WHO criteria)

- Normal BMD is defined as a BMD Z-score ≥ -1
- Osteopenia is defined as a BMD Z-score between -1 and -2.5
- Osteoporosis is defined as a BMD Z-score ≤ -2.5
- Low bone mass=osteopenia and osteoporosis (Z-score < -1)

Statistical analysis

Baseline characteristics were presented by descriptive statistics. The difference in characteristics between normal and low bone mass groups were compared by using Fisher's exact test for categorical data, unpaired t-test for continuous data with normal distribution, and Mann-Whitney U test for continuous data with non-normal distribution. Correlations among continuous data were analyzed by Pearson's correlation coefficient. The *P*-value < 0.05 was considered statistical significance. All analysis was performed using PASW Statistics 18.0 (IBM Corp.)

Results

- Mean hemoglobin and serum ferritin levels were 8.9 ± 0.9 g/dL and 211.6 ± 145.4 ng/mL, respectively (Table 1).

Table 1. Baseline demographic, hematological, biochemical, bone age and BMD data of 22 adolescents with non-transfusion dependent (NTD) Hb E/β thalassemia

Baseline Data	Mean ± SD.	Median (Min, Max)
Age (years)	15.3 ± 1.5	15.1 (13.2, 20.0)
Weight (kg)	45.8 ± 9.2	45.1 (28.1, 67.2)
Height (cm)	159.3 ± 10.0	158.0 (135.7, 182.7)
Weight Z-score	-0.4 ± 1.1	-0.6 (-2.8, 1.8)
Height Z-score	-0.1 ± 1.8	-0.1 (-3.0, 5.3)
Age at the diagnosis (years)	5.6 ± 3.2	5.5 (0.4, 13.0)
Duration of the disease (years)	9.6 ± 2.9	8.7 (4.4, 15.8)
Average hemoglobin over 6 months (g/dL)	8.9 ± 0.9	9.1 (7.3, 10.6)
Average SF over 2 years (ng/mL)	211.6 ± 145.4	158.3 (38.1, 656.3)
LPI (μM)	0.85 ± 2.29	0.41 (-1.50, 5.63)
NTBI (μM)	1.11 ± 0.94	0.76 (0.26, 3.89)
Serum 25-OHD (ng/mL)	22.1 ± 5.4	20.83 (14.7, 32.0)
Bone age (years)	14.3 ± 1.9	14.0 (11.0, 19.0)
Bone age Z-score	-0.4 ± 1.3	-0.5 (-3.2, 2.8)
BMDTB Z-score adjusted for bone age	-0.4 ± 1.6	-0.3 (-3.6, 3.5)
BMDLS Z-score adjusted for bone age	-1.0 ± 1.4	-1.2 (-3.5, 3.3)

- The prevalence of short stature, delayed puberty and low bone mass are 9.1%, 9.1% and 63.6% (L2-L4; Fig 1), respectively.

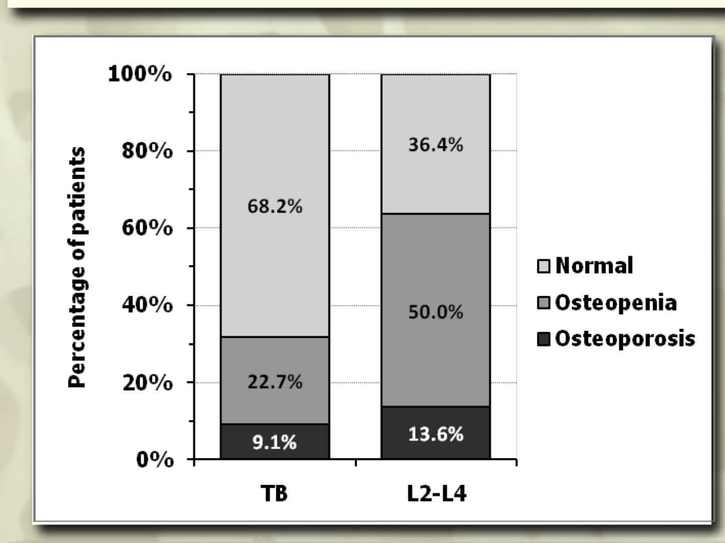

Figure 1. The percentages of NTD Hb E/β-thalassemic adolescents with normal BMD, osteopenia and osteoporosis are shown. BMD of the L2-L4 and the total body (TB) adjusted for bone age were measured. The prevalence of low bone mass (osteopenia and osteoporosis) was high (at L2-L4; 63.6% and TB; 31.8%). L2-L4 spines are more affected by low bone mass than the total body.

Table 2. Comparison of baseline demographic, hematological data and serum 25-OHD levels between low bone mass vs. normal BMD groups measured at total body adjusted for bone age

Baseline Data	Low bone mass (N=7)	Normal (N=15)	*P*-value
Weight Z-score	-0.2 ± 1.0	-0.5 ± 1.2	0.482
Height Z-score	-0.1 ± 1.3	-0.1 ± 2.0	0.932
Age at the Diagnosis (years)	5.8 ± 3.9	5.6 ± 2.9	0.880
Duration of the disease (years)	9.3 ± 2.8	9.7 ± 3.1	0.765
Hemoglobin (g/dL)	8.3 ± 0.9	9.2 ± 0.6	***0.014****
Serum ferritin (ng/mL)	282.2 (108.7, 656.3)	157.5 (38.1, 497.1)	0.185
LPI (μM)	-0.9 (-1.5, 5.6)	1.3 (-1.5 to 4.6)	0.588
NTBI (μM)	0.9 (0.5, 3.9)	0.7 (0.3, 3.4)	0.485
Serum 25-OHD (ng/mL)	21.8 ± 5.1	22.2 ± 5.8	0.913

*$P < 0.05$; statistical significance. Data are presented in mean±SD or median (min, max) depending on data distribution (normal or non-normal distribution, respectively).

- Mean Hb levels among patients with low bone mass were significantly lower than those with normal BMD measured by BMDTB adjusted for bone age. (8.3±0.9 vs. 9.2±0.6 g/dL, *P*=0.014; Table 2).
- We found no difference of baseline demographic, hematological data and serum 25-OHD levels between low bone mass vs. normal BMD groups measured at L2-L4 BMD adjusted for bone age (data not shown).

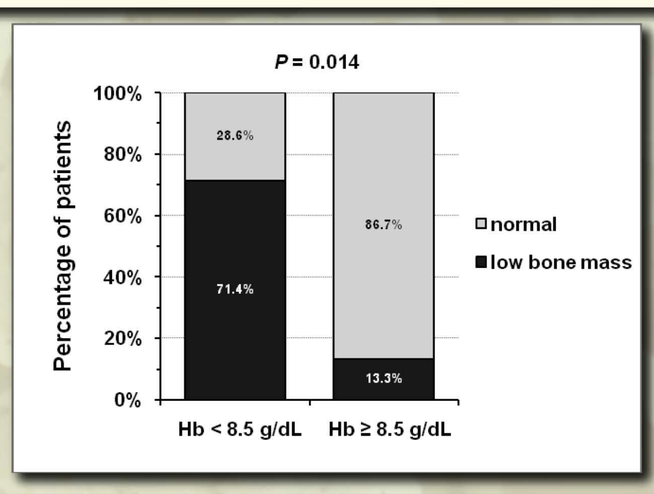

Figure 2. The percentage of patients with low bone mass (measured at BMDTB adjusted for BA) among patients with mean Hb levels of < 8.5 g/dL is significantly higher than those with mean Hb level of ≥ 8.5 g/dL. (71.4% vs. 13.3%, *P*=0.014). However, the percentages of patients with low bone mass (measured at BMDLS adjusted for BA) are not different between both groups (71.4% vs. 60.0%, *P*=1.000; data not shown).

- Average hemoglobin level correlates significantly with L2-L4 (r=0.59, *P*=0.004) and total body BMD Z-score adjusted for BA (r=0.51, *P*=0.015)
- We found no correlation between LPI and NTBI vs. serum ferritin, BMDLS and BMDTB adjusted for bone age.

Conclusion

- To the best of our knowledge, this is the first study to show that low bone mass is highly prevalent among adolescents with NTD Hb E/β-thalassemia.
- Our findings provide important clinical implications for the management of these NTD patients.
- It appears that low bone mass is associated with lower level of hemoglobin but not the level of iron overload.
- Therefore these NTD patients should be comprehensively evaluated and receive appropriate management for a long-term better bone health.
- Physicians should be aware of a high risk of low bone mass among NTD patients.

Acknowledgments

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References

1. Nakavachara P, Viprakasit V. Adrenal insufficiency is prevalent in Hb E/β thalassemia pediatric patients irrespective of their clinical severity and transfusion requirement. Clin Endocrinol (Oxf) 2013;79(6):776-83.
2. Nakavachara P, Viprakasit V. Children with hemoglobin E/β-thalassemia have a high risk of being vitamin D deficient even if they get abundant sun exposure: a study from Thailand. Pediatr Blood Cancer 2013;60(10): 1683-8.
3. Nakavachara P, Pooliam J, Weerakulwattana L, Manorompatarasarn R, Kiattisakthavee P, Chaichanwattanakul K, et al. A normal reference of bone mineral density (BMD) measured by dual energy X-ray absorptiometry in healthy Thai children and adolescents aged 5-18 years: a new reference for Southeast Asian populations. PLoS One. 2014;9(5):e97218.doi:10.1371/journal. pone.0097218.